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Retroperitoneal Fibrosis as a Cause of Fever of Undetermined Origin

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A CONSULTING RHEUMATOLOGIST is sometimes asked to offer his expertise in seeking the cause of a multisystem illness that includes fever, arthralgias, myalgias, anorexia, weight loss, anemia and elevated sedimentation rate. Invariably, consultants in hematology, oncology, endocrinology, gastroenterology and infectious diseases have eliminated illnesses that would fall primarily within their domain. Almost as an afterthought, a rheumatologist is called in to "rule out vasculitis" or "exclude an evolving connective tissue disease." The present case report and discussion emphasize another entity whose prodrome can mimic a multitude of systemic illnesses. Though well described in the surgical literature, it merits more critical attention by internists and rheumatologists in their efforts to offer a more comprehensive differential diagnosis in the workup of a chronically ill patient.

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Report of a Case

A 21-year-old Marine was in excellent health until late October 1979 when a sensation of fullness in the right ear developed, followed by a temperature rising to 38.9°C (102°F), nonshaking chills, anorexia and fatigue. Studies were done at the medical clinic and a diagnosis of right-sided otitis media was made. Ampicillin and erythromycin were prescribed sequentially without improvement. His fever persisted accompanied by arthralgias of the elbows, wrists, knees and ankles as well as a retrobulbar headache without photophobia. Because the symptoms persisted, the patient was admitted to hospital at the Naval Regional Medical Center, Camp Lejeune, North Carolina, on November 5, 1979. On admission, a physical examination documented a temperature of 38°C (100.4°F). There were multiple, small, nontender posterior, cervical and supraclavicular nodes. Liver span was 12 cm and the spleen was soft, nontender and palpable 2 cm below the left costal margin. Humeroulnar joints and wrists were tender to palpation without obvious synovial thickening. Initial laboratory test results included a hematocrit of 30 percent, with a leukocyte count of 10,200 per cu mm and a normal differential. Platelet count was 178,000 per cu mm. Westergren sedimentation rate was 130 mm per hour. A peripheral blood smear was hypochromic. The following studies gave normal or negative findings: SMA-18, hepatitis-associated antigen, mononucleosis spot test, cold agglutinins, VDRL, Coombs direct and indirect tests, latex fixation, fluorescent antinuclear antibody (FANA) and analysis of the urine. Multiple blood cultures were negative. Purified protein derivative-standard (PPDS) and streptokinase-streptodornase (SKSD) skin tests were nonreactive. Additional studies included a bone marrow aspirate, which showed myeloid and megakaryocytic hyperplasia. A left posterior cervical node biopsy showed lymphoid hyperplasia. Adult Still disease was considered a reasonable possibility at this time, and high-dose salicylate therapy was initiated. The fever abated somewhat but the hematocrit decreased to 23 percent, with a hypo-

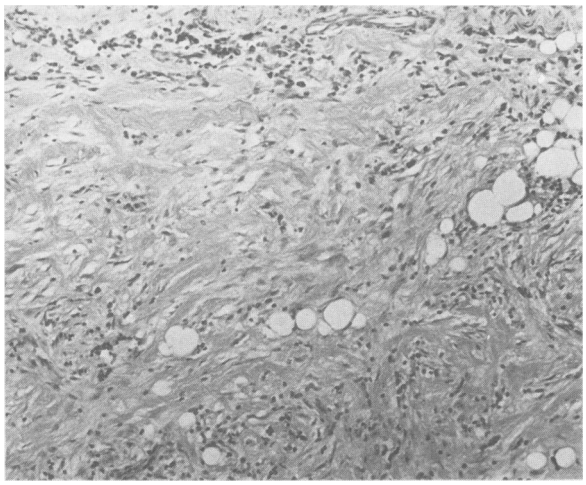

Figure 1.—A retroperitoneal biopsy specimen showing diffuse fibrosis with entrapment of adipose tissue and a lymphoplasmacytic infiltrate with eosinophils (reduced from approximately 100×).

chromic, microcytic blood smear. There was no evidence of loss of blood. Because the symptoms persisted, the patient was transferred to the Naval Regional Medical Center, Portsmouth, Virginia, where he remained in hospital from 11 December 1979 to 21 February 1980. Vital signs on admission were normal with the exception of a temperature of 38.6°C (101.4°F). A spleen tip was palpable. During his stay in hospital, a hectic fever persisted in association with drenching night sweats. An exhaustive workup was initiated. Serological studies gave normal or negative findings for antinuclear antibody (ANA), latex fixation, thyroid panel, serum B_{12}, serum folate, C-3, C-4, CH-50, toxoplasmosis and cytomegalovirus titers, and α-fetoprotein; a urine test for human chorionic gonadotropin was negative. The alkaline phosphatase level was 254 units (normal 40 to 115). An SKSD skin test was reactive. An x-ray study of the chest, sinus series and intravenous pyelogram (IVP) showed no abnormalities. A liver-spleen scan and gallium scan demonstrated hepatosplenomegaly without focal defects. A bone scan as well as upper gastrointestinal and small bowel studies showed no abnormalities. An abdominal computed tomographic (CT) scan gave negative results. Procedural studies, including endoscopy, proctosigmoidoscopy, lumbar puncture and percutaneous liver biopsy, gave negative results as well. A bone marrow aspirate again showed hyperplasia of all the cell lines. During his time in hospital, the patient remained anorectic and febrile and lost 20 pounds. In view of his clinical deterioration, with spiking fevers and anemia that required transfusion, an exploratory laparotomy was done on January 24, 1980. The preoperative diagnosis was abdominal lymphoma.

At laparotomy, a large mass (6×8×4 cm) was found in the rectosigmoid area at the brim of the sacrum, inferior to the rectum, appearing adherent to the bowel but easily separated. Frozen sections indicated fibrosis and inflammation. Permanent sections showed changes consistent with retroperitoneal fibrosis, with areas of dense refractile collagen laid down in a haphazard arrangement (see Figure 1). The fibrosis was accompanied by an inflammatory infiltrate composed of lymphocytes, plasma cells and eosinophils. Some sections showed destruction and entrapment of adipose tissue. A prominent feature of the biopsy specimens was a chronic vasculitis which appeared to be primarily centered around venules (Figure 2). Immunofluorescent studies were not done on the unfixed specimen. Subsequently, immunoperoxidase studies were obtained on the formalin-fixed tissue and were negative. Biopsies of the liver, spleen and mesenteric nodes gave negative results. A diverting colostomy was carried out. Postoperatively, the patient continued to have spiking temperatures from 39° to 40°C (102.2° to 104°F). On February 12, after all special stains as well as fungal and acid-fast bacilli cultures were reported as negative, prednisone therapy was initiated in a dosage of 15 mg four times a day. Fever resolved within 48 hours. Corticosteroid therapy was gradually tapered over 3½ months and discontinued at the end of May. The hematocrit at that time was 44 percent, with a normal sedimentation rate. During this time, the patient regained 20 pounds. The colostomy was revised on June 30 and the patient has continued to remain asymptomatic and afebrile.

Discussion

Since Ormond established idiopathic retroperitoneal fibrosis as a clinical entity in 1948,[1] more than 600 cases have been reported in the medical and surgical literature. Most cases, however, have emphasized obstructive phenomena as well as diagnostic and therapeutic approaches, with less attention given to systemic manifestations. That the latter feature may be unfamiliar to many general internists and medical subspecialists, is suggested by the fact that the four largest reviews of retroperitoneal fibrosis have appeared in the

surgical and radiological literature,[2-5] with constitutional symptoms given only passing reference in recent editions of two major medical texts.[6,7] The entity is not even mentioned in the most recent edition of a standard rheumatology text.[8]

The critical importance of retroperitoneal fibrosis to internists in general, and to rheumatologists in particular, is amply illustrated by both its propensity to occur in the fifth and sixth decades and its varied presenting signs, symptoms and serological test findings. The most prominent of these are: back pain,[1] abdominal pain,[9] intermittent claudication,[10] headache,[11] Raynaud phenomenon,[12] hypertension,[13] pericardial friction rub,[14,15] pleural effusion,[15] splenomegaly,[3] fever, weight loss, anorexia, increased sedimentation rate and hyperglobulinemia.[16] Certainly, a reasonable differential diagnosis of the above might include the following: granulomatous diseases such as tuberculosis or sarcoidosis,[17] adult Still disease,[18] systemic lupus erythematosus,[19] periarteritis nodosa,[20] giant cell arteritis,[21] Whipple disease,[22] T-3 toxicosis,[23] atrial myxoma,[24] bacterial endocarditis[25,26] and neoplasm.[27] Many of these illnesses, of course, respond partially or completely to corticosteroid therapy. One cannot help but wonder whether some cases of biopsy-negative giant cell arteritis, ANA-negative lupus, and presumptive adult Still disease (without the characteristic rash) have represented undiagnosed retroperitoneal fibrosis.

Many publications have suggested more than a coincidental association between retroperitoneal fibrosis and connective tissue diseases.[28-31] Since the relationship between methysergide maleate (Sansert) and retroperitoneal fibrosis was extensively reviewed in 1966,[32] many have postulated that the condition represents a hypersensitivity response to a variety of antigens including bacterial, fungal, tuberculous, tumor-associated and drug-hapten combinations.[2,3,16] Support for this premise can be found in a number of case reports documenting a small-vessel vasculitis with all lesions in a similar stage of evolution.[12,15,33,34] Additionally, several recent reports have documented the presence of immunofluorescence[35] as well as immune complex glomerulonephritis with IgG and C-3 deposition.[36] In several instances, connective tissue illnesses have antedated retroperitoneal fibrosis by many years or have been associated with Dupuytren contracture,[37] Peyronie disease,[15,38] idiopathic mediastinal fibrosis,[39,40] Riedel thyroiditis,[39,41] and pulmonary fibrosis,[12,39] further supporting a localized response in a susceptible host to chronic antigenic challenge. Histopathological studies obtained earlier in the illness have consistently demonstrated an intense infiltration of mononuclear cells, predominantly lymphocytes, plasma cells and eosinophils.[11] Biopsy specimens obtained later in the disease process have demonstrated a predominantly fibrotic change.[5] The encouraging responses to corticosteroids in the early cellular phase are all compatible with a primary immune mechanism.

The present case report is most intriguing because it illustrates another cause of fever of undetermined origin in adults. Although another publication indirectly alludes to this type of presentation,[34] retroperitoneal fibrosis as the cause of a prolonged fever was not mentioned in several

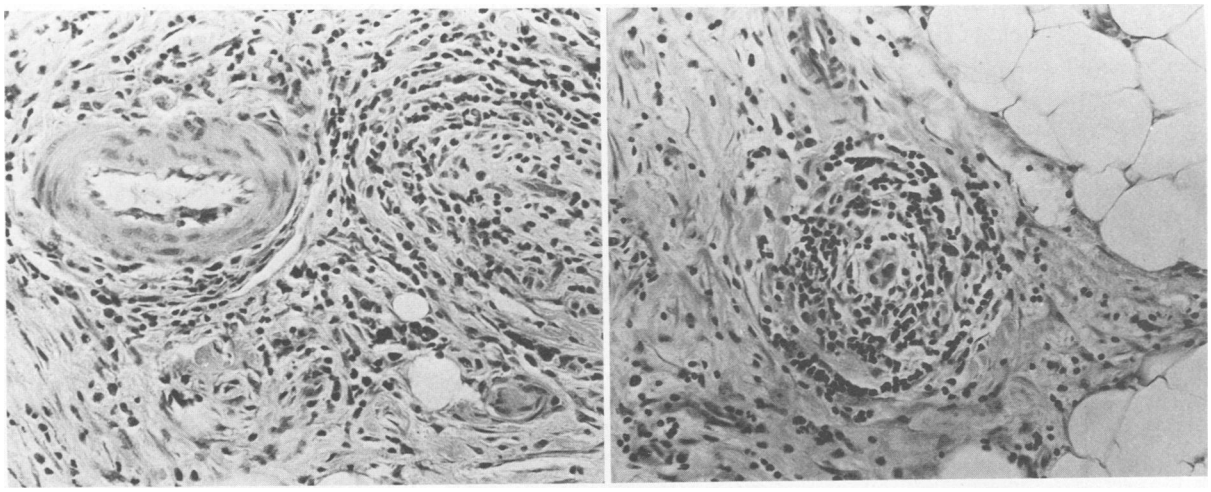

Figure 2.—Left, Area of vasculitis showing minimal involvement of a small arteriole and obliterative venulitis. **Right,** Obliterative venulitis with many plasma cells and lymphocytes (reduced from approximately 400×).

large reviews of fever of undetermined origin in adults and children.[42-44] While our patient's workup was careful and systematic, the diagnosis was not suspected before laparotomy. In this instance, the IVP failed to show the classic triad of medial deviation of the ureters, bilateral ureteral narrowing, and dilatation of calices and pelvis.[45] Sophisticated noninvasive tests were not helpful.[38,46] In retrospect, had a barium enema study been done and had the CT scan included the pelvis, the rectosigmoid mass undoubtedly would have been discovered before laparotomy. Fortunately, the patient's response to corticosteroid therapy was excellent.

As in many connective tissue illnesses (such as Wegener granulomatosis, giant cell arteritis and polyarteritis nodosa), early diagnosis is critically important to prevent death or permanent damage to organs. It is hoped that greater awareness of retroperitoneal fibrosis as a cause of fever of undetermined origin may facilitate early diagnosis and a favorable response to corticosteroid therapy. Unfortunately, current guidelines for dosage and duration of such steroid therapy are imprecise and the long-term prognosis is unknown.[47,48] Further investigations are needed to solve these problems.

Summary

Idiopathic retroperitoneal fibrosis (Ormond disease) has been recognized as a cause of obstructive uropathy for more than 70 years. Less well known is its association with profound constitutional disease, as well as with many connective tissue illnesses. Recent observations of dramatic clinical responses to corticosteroid therapy as well as pathological studies confirming intense perivascular inflammation and positive immunofluorescence argue persuasively for immune complex-mediated injury. This case report establishes one more cause for fever of undetermined origin and reviews the clinical features of an entity that should be familiar to every internist and rheumatologist.

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Treatment of Agenesis of the Diaphragm and Esophageal Crura

An 18-Year Follow-up

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WHEN COMPLETE PROSTHETIC REPLACEMENT of a missing vital body part with an implant is done for the first time, serious questions arise: Will the prosthesis expand as the implant grows? If not, will bodily deformity result from the restrictions, thereby making eventual replacement of the prosthesis necessary?

In considering a prosthetic implant to replace a missing left diaphragm and esophageal crura, it was felt that a porous mesh prosthesis rather than a solid one would adapt best to an infant's growth.[1] This hypothesis was supported by experiments in animals[2] in which growth of surrounding tissues into mesh implants suggested that such a prosthetic implant would continue to change in size and contour in accordance with the animal's growth. Studies by Debakey and co-workers[3,4] had shown that a porous Dacron graft used to replace the aorta of a patient had enlarged with the patient's own growth. It appeared that secondary replacement would not be necessary. This approach, it was hoped, could be applied to the replacement of other bodily parts. An 18-year follow-up report of such a case, examining these points, is presented.

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Report of a Case

A newborn infant presented 18 years ago in a moribund cyanotic state with a scaphoid abdomen and poor chest expansion on both sides but more limited on the left. Breath sounds were absent on the left side of the chest and no masses were palpable in the abdomen. X-ray studies showed abdominal viscera in the left side of the chest, with a compression of the right lung that was consistent with a large congenital diaphragmatic hernia. An emergency laparotomy was done 12 hours after birth, and instead of a partial diaphragmatic defect, a complete absence of the left diaphragm and esophageal crura was found. Also, the stomach and large portions of the small bowel and colon were protruding into the chest, pushing the mediastinum to the right (Figure 1). With not even a remnant of diaphragm, it was apparent that some type of implant was necessary. With the use of a solid prosthesis or impermeable fine mesh, it was probable that, even with a successful implant, the prosthesis might have to be changed later as the infant grew. It was hoped that a porous mesh Dacron graft would enlarge with the child's growth, making this replacement unnecessary.

A preclotted graft was sewn to the periosteum of the ribs and the synthetic esophageal crura, sutured to the small neonatal esophagus, fashioned to keep the stomach in the abdominal cavity. An effective air-tight seal soon formed a new diaphragm, and within two weeks the rudimentary lung expanded and the infant was discharged in a satisfactory condition on the 19th postoperative day.

The mesh diaphragm and esophageal crura became a vital part of the child's own tissues and expanded with the child's normal growth pattern. Periodic x-ray studies of the chest showed that the synthetic graft was continuing to expand as the child grew; thus, deformity was prevented. At 18 months of age, x-ray studies (after oral administration of barium) showed that the synthetic mesh esophageal crura, which had now become an inherent part of the child's tissues, were continuing to function to prevent esophageal reflux (Figure